REMARKS

Interview request

Applicants respectfully request a telephonic interview after the Examiner has reviewed the instant response and amendment. Applicants request the Examiner call Applicants' representative at 858 720 5133. The outstanding office action is non-final because new rejections not necessitated by amendment were added.

Status of the Claims

Pending claims

Claims 1 to 5, 16 to 18, 20 to 23, 40, 41 to 55, 61 to 63, 65, 67, 68, 77, 78, 80 to 82, 85, 88 to 92, 97 to 102 and 107 to 125 are pending. Claims 42 to 55, 61 to 63, 65, and 88 to 92 remain withdrawn as being drawn to a non-elected invention. Thus, claims 1 to 5, 16 to 18, 20 to 23, 40, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 107 to 125 are pending and under consideration.

Claims added and deleted in the instant amendment

Claim 126 is added, and claims 17, 18, 77, 78, 85, 97, 112 and 118 to 125 are deleted, without prejudice or disclaimer. Thus, after entry of the instant amendment, claims 1 to 5, 16, 20 to 23, 40, 41 to 55, 61 to 63, 65, 67, 68, 80 to 82, 88 to 92, 98 to 102, 107 to 111, 113 to 117, and 126, will be pending and under consideration.

Claim only objected to

Applicants thank the Examiner for noting claim 2 is only objected to.

Outstanding Rejections

Claims 78, 109 and 118 to 125 are rejected under 35 U.S.C. §112, second paragraph. Claims 107, 108, 112 and 120 are rejected under 35 U.S.C. §112, first paragraph, written description requirement, for allegedly lacking support in the specification. Claims 1, 3 to 5, 16 to 18, 20 to 23, 40, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 107 to 125, are rejected under 35 U.S.C. §112, first paragraph, written description and enablement requirements. Claims 29, 153, 154, 160 and 173 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Robertson et al., PCT publication WO 97/30160, international publication date August 21, 1997 (hereinafter

"Robertson"). Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the amended claims. For example, support for polypeptides of the invention having esterase activity at extreme temperatures, e.g., temperatures above 100°C, or below 0°C, or other extreme conditions, can be found, inter alia, on page 21, paragraph 98 (see, e.g., line 9 of that paragraph). Support for polypeptides of the invention having esterase activity comprising hydrolase activity, for example, polypeptides of the invention encompassing enzymes capable of hydrolyzing ester groups to organic acids and alcohols, can be found, inter alia, on page 6, paragraph [0038]. Accordingly, no new matter is added by the instant amendment.

Priority and objections under 35 USC §132(a)

The instant amendment perfects the instant application's claim to priority to PCT/US97/02039, filed February 11, 1997, published in English on August 21, 1997 as WO 97/30160, as discussed in the "Decision on Petition under 37 CFR 1.78(a)(3)", mailed May 28, 2004. In brief, the Decision noted that there were two items that needed further correction before the Petition to add the priority document could be granted. First, the specification is amended to comply with 35 USC §120 and 37 CFR §1.78(a)(2)(i), by adding that this application claims the benefit of and is a continuation-in-part of U.S. Application Serial No. 09/382,242, filed August 24, 1999, now pending. Second, after entry of the instant amendment the application no longer incorporates by reference the newly added priority document. Finally, a corrected (substitute) Application Data Sheet (ADS) is being concurrently submitted with this filing.

Informalities – claim objections

The Office objected to claims 3 and 5, because it was alleged that the term "n" is not an abbreviation for any known unit of mass. However, Applicants respectfully note that one of skill in the art at the time of the invention would have understand that use of the term "n" in the context of

the specification would mean "ng"; in fact, use of the term "n" was an inadvertent typographical error.

The instant amendment addresses the claim objections as set forth in the OA on page 5, lines 10 to 19, of the OA. Claim 77 is deleted, without prejudice or disclaimer.

Issues Under 35 U.S.C. § 112, Second Paragraph

Claims 78, 109 and 118 to 125 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The instant amendment addresses the issues as set forth in the OA on page 5, line 20, to page 6, line 22, of the OA. Claims 78 and 118 to 125 are deleted, without prejudice or disclaimer.

Issues Under 35 U.S.C. § 112, First Paragraph - Written Description

Support in the Specification

Claims 107, 108, 112 and 120 are rejected under 35 U.S.C. §112, first paragraph, written description requirement, for allegedly lacking support in the specification.

In particular, the rejection of claims 107 and 108 is maintained for allegedly not providing support for enzymes of the invention catalyzing transesterification or acidolysis reactions. Applicants respectfully transverse for reasons set forth in their previous response. However, merely to expedite prosecution, claims 107 and 108 are amended in the instant response.

Possession of the Claimed Invention

The rejection of claims 1, 3 to 5, 16 to 18, 20 to 23, 40, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 107 to 109, is maintained, and claims 110 to 125, are newly rejected, under 35 U.S.C. §112, first paragraph, written description requirement, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention.

Esterase activity

Claims 1, 22, 40 and 107 to 109 are directed to, inter alia, polynucleotides having 90% sequence identity to SEQ ID NO:26, and encoding a polypeptide with an esterase activity. The

Office alleges, inter alia, that because there is a wide variety of functions encompassed within the term "esterase activity", and enzymes that can cleave one ester bond will not cleave all ester bonds, the term encompasses functionally unrelated esterase-encoding nucleic acids. Thus, it is alleged that because the specification discloses only a single species of a claimed genus, the specification did not reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention.

Applicants respectfully maintain that the specification did reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention. As discussed in their previous response, at the time of the invention one skilled in the art would have understood the meaning and scope of the term esterase activity, which includes the hydrolysis or synthesis of an ester. The hydrolysis of an ester bond is a specific chemical reaction recognized in the art and easily assessed using routine methods, as evidenced by the declaration of Dr. Jay Short, already of record.

The specification as filed provided adequate written description for the full scope of the term esterase activity. For example, paragraph [0003], page 1, of the specification states:

> [0003] A principle example of esterases are the lipases, which are used in the hydrolysis of lipids, acidolysis (replacement of an esterified fatty acid with a free fatty acid) reactions, transesterification (exchange of fatty acids between triglycerides) reactions, and in ester synthesis.

These are not new esterase activities, but are well established esterase activities. Polypeptides of the invention having esterase activity comprising hydrolyzing ester groups to organic acids and alcohols, can be found, inter alia, on page 6, paragraph [0038]:

> [0038] The present invention relates to esterases and polynucleotides encoding them. As used herein, the term "esterase" encompasses enzymes having hydrolase activity, for example, enzymes capable of hydrolyzing ester groups to organic acids and alcohols.

Accordingly, the specification disclosure is sufficient to demonstrate that the inventors had possession of the claimed compositions at the time of filing.

The Office alleges that the written description requirement is not met because some esterases may work on some compounds, but not on others. However, Applicants respectfully submit that the written description standard does not require that all enzymes within the scope of the claimed genus act upon the same substrates, but rather is whether the claimed invention was sufficiently described in the specification such that one of ordinary skill in the art would have been able to ascertain the scope of the claims with reasonable clarity to recognize that Applicants' were in possession of the claimed invention at the time of filing.

The application does not need to describe the claim limitations exactly (e.g., exactly describe all the substrates that can, or cannot, be hydrolyzed by any particular specie member of the claimed genus), but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that Applicants invented and had possession of the claimed subject matter. Whether the specification clearly shows that Applicants were in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the Applicant was in possession of the claimed species is sufficient. See Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); MPEP §2163 II.A.3(a)(i)(C)(2), pg 2100-173, 8th ed., rev. 2, May 2004.

Applicants respectfully submit that, as discussed above, a combination of identifying characteristics that distinguished the claimed invention from other materials was sufficiently disclosed to distinguish the claimed invention from other materials, thus leading one of skill in the art to the conclusion that Applicants were in possession of the claimed genus of esterase-encoding nucleic acids. For example, the physico-chemical properties of the claimed genus of esterase-encoding nucleic acids was described; the scope and meaning of the term "esterase activity" was

described in the specification; and, as evidenced by Dr. Short's declaration, the level of skill and knowledge in the art regarding esterases was very high. Accordingly, the skilled artisan could have reasonably concluded that Applicant had possession of the claimed genus of esterase-encoding nucleic acids.

Fragments and Variants of the Exemplary Nucleic Acid

Claims 3 to 5, 16 to 18, 20, 21, 23, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 110 to 125, are rejected under the written description requirement of section 112. As fragments and variants are separate issues, Applicants will discuss each in turn.

Variants of the Exemplary Nucleic Acid

The Office is concerned that these claims are not limited to polynucleotides having at least 90% sequence identity to SEQ ID NO:26 that encode polypeptides with esterase activity, see page 9, line 18, to page 13, line 6, of the OA, particularly noting the sentence spanning pages 12 and 13. The instant amendment addresses this issue. Claims 3 to 5, as currently amended, are directed to, inter alia, isolated or recombinant nucleic acids that hybridize to a nucleic acid comprising a sequence as set forth in SEQ ID NO:26, and encoding a polypeptide having an esterase activity.

While Applicants believe the instant amendment addresses the Office's concerns regarding this issue, they wish to address and clarify some comments made in the OA about the specification description. The Office alleged, inter alia, that the specification provided no description of the structure and function the modified polypeptide sequences encompasses by the claims (see page 10, lines 4 to 6, of the OA); that no information, beyond characterization of SEQ ID NO:26, was provided by the specification (page 10, lines 7 to 10, of the OA); noted the large size of the genus (page 10, lines 18 to 19, of the OA); and, referred to the USPTO written description guidelines (page 11, lines 3 to 6, of the OA).

Applicants believe the instant amendment addresses the Office's concerns about the size of the genus, as noted above. Regarding the remaining concerns, Applicants respectfully submit that describing a genus of polynucleotides in terms of physico-chemical properties (e.g., a % sequence identity or stringent hybridization to an exemplary nucleic acid or polypeptide, e.g., SEQ

ID NO:26 or SEQ ID NO:36) and function (e.g., encoding a polypeptide having esterase activity) satisfies the written description requirement of section 112, first paragraph.

Applicants respectfully aver that the disclosed nucleic acid and polypeptide species of the claimed invention, SEQ ID NO:26 and SEQ ID NO:36, are sufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genera. Applicants emphasize that the claimed genera are defined in terms of shared physical and structural properties. As discussed in detail, below, the claimed genus of nucleic acids are all structurally related, have defined structure function relationships, and have an expressly delimited structure.

Both the Patent Office and the Federal Circuit set forth conditions where a single species is sufficient to put one of skill in the art in possession of the attributes and features of all species within a genus, where the genus is defined in terms of shared physical and structural properties with the single species. The referenced USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first paragraph, state that a description of a genus of polynucleotides in terms of its physico-chemical properties, e.g., a % sequence identity, to a single exemplary species, and a common function satisfies the written description requirement of section 112, first paragraph, for the genus of polynucleotides.

In Example 14 of the Guidelines (a copy of which is attached as Exhibit A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The analysis of Example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The Guidelines conclusion states that the disclosure

meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the genus of claimed nucleic acids are described by structure (the exemplary SEQ ID NO:26 and SEQ ID NO:36), a physico-chemical property (a percent sequence identity to an exemplary sequence or stringent hybridization to an exemplary nucleic acid) and function (having esterase activity). In one aspect, all species of the genus of claimed nucleic acids must have at least 90% or more sequence identity to a sequence as set forth in SEQ ID NO:26. Because the USPTO guidelines recognize that written description is met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity, stringent hybridization) and a defined function, the genus of polypeptides used in the claimed methods also meet the written description requirements of section 112.

The Federal Circuit has applied the written description requirement of the first paragraph of § 112 to inventions in the field of biotechnology. See University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). The genus of polypeptides used in the claimed methods also fully complies with the requirements for written description of a genus as set forth in University of California v. Eli Lilly & Co.. In Lilly, the Court stated that, "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs....*or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406. The Lilly court explained that

> In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass. Accordingly, such a formula is normally an adequate description of the claimed genus. . . [H]owever, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as

> one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is.

Id. at 1568, 43 USPQ2d at 1406.

The Lilly court also stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405. Finally, the court addressed the manner by which a genus of cDNAs might be described. "A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." Id. at 1568, 43 USPQ2d at 1406.

The instant claims clearly set forth specific structural and physical characteristics of the claimed esterase-encoding or esterase-identifying nucleic acids. In one aspect, the genus of nucleic acids all encode polypeptides having esterase activity and a specific physical characteristic, e.g., a % sequence identity to the exemplary SEQ ID NO:26, or, hybridization to SEQ ID NO:26. Therefore, the genus of claimed esterase-encoding or esterase-identifying nucleic acids is defined via shared physical and structural properties in terms that "convey with reasonable clarity to those skilled in the art that Applicant, as of filing date sought, was in possession of invention." (Vas-Cath Inc. V. Mahukar, 19 USPQ2d 1111, (Fed Cir. 1991)).

The Federal Circuit has also addressed the written description requirement in the context of DNA-related inventions. See Enzo Biochem. Inc. v. Gen-Probe Inc., 296 F.3d 1316, 63 USPQ2d 1609 (Fed. Cir. 2002). The Enzo court adopted the standard that "the written description requirement can be met by 'showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or some combination of such characteristics.'" [Emphasis added] Id. at 1324, 63 USPQ2d at 1613. The court in Enzo adopted its standard from the USPTO's Written Description Examination Guidelines. See 296 F.3d at 1324, 63 USPQ2d at 1613 (citing the Guidelines, note discussion, above). The Guidelines apply to proteins as well as DNAs. The Enzo court also stated:

> Similarly, in this court's most recent pronouncement, it noted:
>
> > More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)]. Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the functions of the enzymes encoded by the claimed nucleic acids are sufficiently correlated to a particular, known structure (the exemplary sequence SEQ ID NO:26 or SEQ ID NO:36) and a physical (physico-chemical) property (percent sequence identity or stringent hybridization). Accordingly, the species of claimed nucleic acids, and polypeptides of the invention, were defined via shared physical and structural properties in terms that conveyed with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Subsequence, or Fragments, of Claimed Nucleic Acids

Claims 3 to 5, 16 to 18, 20, 21, 23, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 110 to 125, are rejected under the written description requirement of section 112, for not containing any disclosure of the structure and function of all the polynucleotide sequences derived from SEQ ID NO:26, including fragments (see, e.g., page 10, lines 10 to 14) of the OA.

Applicants respectfully aver that the structure and function of the genus of esterase-encoding or esterase-identifying polynucleotide sequences having at least 90% sequence identity to SEQ ID NO:26, or capable of hybridizing to SEQ ID NO:26 under specific conditions, were defined via shared physical and structural properties in terms that conveyed with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Regarding species members of the claimed genus that encompass subsequences, or fragments, of the exemplary sequences of the invention, Applicants respectfully maintain that these functional subsequences (fragments) are sufficiently described in the specification so that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing.

The subject matter of the claim need not be described literally (i.e., using the same terms or *in haec verba*) in order for the disclosure to satisfy the description requirement. See also MPEP §2163 II.A.3(a)(i)(C)(2), pg 2100-173, 8th ed., rev. 2, May 2004. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that applicants invented the claimed subject matter. In re Herschler, 591 F.2d 693, 700, 200 USPQ 711,717 (CCPA 1979). See also Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

Applicants respectfully submit that claimed subsequences are described with reasonable clarity even though the limitations regarding the length of active subsequences are not exactly described. The application does not need to describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that Applicants invented and had possession of the claimed subject matter. As noted above, whether the specification clearly shows that Applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of

factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the Applicant was in possession of the claimed species is sufficient.

Applicants respectfully submit that consideration of a number of factors leads to a factual determination that the subsequences of the exemplary enzyme of the invention would lead one of skill in the art to the conclusion that Applicant was in possession of the claimed species of functional subsequences. For example, the level of skill and knowledge in the art regarding making fragments of a sequence and testing for activity was very high at the time of the invention. The physical and/or chemical properties of the enzymatically active polypeptides of the claimed invention are sufficiently described, with the exception that the exact length of the subsequences are not specifically delineated. The functional characteristics were described in that all claimed subsequences have esterase enzyme activity or esterase-identifying activity. The method of making the claimed subsequences was well known and routine at the time of the invention. Accordingly, Applicants have disclosed sufficient combination of these identifying characteristics to distinguish the claimed invention from other materials and to lead one of skill in the art to the conclusion that the Applicant was in possession of the claimed genera of functional esterase subsequences.

Accordingly, Applicants respectfully submit that in light of these remarks and the instant amendment the §112, first paragraph, written description rejection can be properly withdrawn.

Issues under 35 U.S.C. § 112, First Paragraph - Enablement

The rejection of claims 1, 3 to 5, 16 to 18, 20 to 23, 40, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 107 to 109, is maintained, and claims 110 to 125, are newly rejected, under 35 U.S.C. §112, first paragraph, enablement requirement.

Claims 1, 3 to 5, 16 to 18, 20 to 23, 40, 41, 67, 68, 77, 78, 80 to 82, 85, 97 to 102 and 107 to 125, are rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement. It is alleged, inter alia, that the specification lacks reasonable enablement for any polypeptide having at least 90% sequence identity to SEQ ID NO:26 and encoding a polypeptide with an esterase activity, or any polynucleotide comprising at least 30 bases of a sequence having 90% identity to SEQ ID NO:26 and encoding a polypeptide with an esterase activity, or any polynucleotide comprising a fragment of SEQ ID NO:26 or encoding fragments of SEQ ID NO:36, or all fragments or variants thereof, or vectors and host cells comprising said nucleic acids for reasons of record (see page 13, line 7, to the last line of page 19, of the OA).

The Office does note that the specification is enabling for polynucleotides encoding SEQ ID NO:36 (see page 13, lines 9 and 10, of the OA).

One of the Office's concerns regards the scope of the invention and the size of the claimed genus (see also the sentence spanning pages 12 and 13, of the OA). As discussed above, the instant amendment addresses this issue. Claims 3 to 5, as currently amended, are directed to, inter alia, isolated or recombinant nucleic acids that hybridize to a nucleic acid comprising a sequence as set forth in SEQ ID NO:26, and encoding a polypeptide having an esterase activity.

Applicants respectfully aver that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, the claimed genus of esterase-encoding polynucleotides – and have provide evidenced and expert declaration to support this argument (see, e.g., Applicants' response of February 11, 2005, pages 14 to 15; and, of November 19, 2003, pages 21 to 23, including Dr. Jay Shorts expert declaration, expressly incorporated herein).

A prima facie case of Lack of Enablement has not been made

However, Applicants respectfully aver that the Patent Office has not met its initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. The art cited by the Office to support its *prima facie* case of lack of enablement is insufficient to rebut the presumptively enabled specification.

In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). See also MPEP §2164.04, rev. 2, May 2004, pg 2100-189.

The Patent Office has cited Guo (2004) Proc. Natl. Acad. Sci. USA 101:9205-9210 ("Guo") (see page 18, lines 3 to 13), to support its *prima facie* case of lack of enablement alleging, inter alia, that it was not routine to screen for multiple substitutions or multiple modifications of the exemplary sequence to additional species within the scope of the claimed genus (see, e.g., page 15, lines 3 to 13). The Office uses Guo to support the allegation that because there is a large number of possible nucleic acid sequence variations, it would take undue experimentation to determine all of the active, versus inactive, species within the claimed genus (that are variants of the exemplary SEQ ID NO:26) (see, e.g., pages 18 and 19, of the OA).

However, the teaching of Guo is insufficient to rebut the presumptively enabled specification and therefore cannot support a *prima facie* case of lack of enablement. Guo developed a mathematical paradigm to quantitate protein tolerance to random sequence changes. Guo's model was developed to understand the probability that a random amino acid replacement will lead to a protein's functional inactivation. While Guo's model does predict that random codon replacement

will generate many inactive variants, in fact, they found 920 "tolerated" or active variants. Thus, Guo actually demonstrates that significant numbers of active variants can be generated using a random mutation and screening protocol.

It is because the Office believes that the amount of screening needed for a random mutation scheme would take undue experimentation that it alleged that to be enabling the specification needed to describe, inter alia, regions of protein structure which may be modified without effecting esterase activity, and a rational and predictable scheme for modifying any amino acid residue with an expectation to obtain the desired (esterase) function. It is also alleged that the specification provides insufficient guidance as to which residues can be changed to generate an active sequence.

Applicants respectfully maintain, for reasons set forth herein, and in their previous responses, that in view of the state of the art at the time of the invention the specification sufficiently enabled how to make and use, including how to screen for, active sequences of the invention using random mutagenesis techniques. Thus, it was not necessary that the skilled artisan pre-establish regions of enzyme structure which may be modified without effecting enzyme activity to make and use the invention. For example, Dr. Short declared, inter alia, that it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with esterase activity to create variants of the exemplary nucleic acid and test them for the expression of polypeptides or peptides having esterase activity. Dr. Short declared that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for esterase activity, was very high. Dr. Short declared that one skilled in the art could have used routine protocols known in the art at the time of the invention, including those described in the instant specification, to screen for nucleic acids encoding polypeptides having a percent sequence identity to SEQ ID NO:26, or active fragments thereof, for esterase activity. Dr. Short declares that was routine to screen for multiple substitutions or multiple modifications of an enzyme-encoding sequence and predictably achieve positive results. Accordingly, it would not have taken undue

experimentation to make and use the claimed invention, including identification of a genus of nucleic acids encoding esterases.

Nevertheless, while not necessary, Applicants respectfully aver that if one skilled in the art desired some structural guidance as to what amino acid substitutions could be made to make the genus of esterase-encoding nucleic acids of the invention, such guidance could be found both in the specification and the state of the art at the time of the invention. For example, the specification provides express guidance regarding what amino acid substitutions could be made to make the genus of esterase-encoding nucleic acids of the invention can be found, e.g., in paragraph [0205], page 49:

> [0205] Conservative substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Typically seen as conservative substitutions are the following replacements: replacements of an aliphatic amino acid such as Alanine, Valine, Leucine and Isoleucine with another aliphatic amino acid; replacement of a Serine with a Threonine or vice versa; replacement of an acidic residue such as Aspartic acid and Glutamic acid with another acidic residue; replacement of a residue bearing an amide group, such as Asparagine and Glutamine, with another residue bearing an amide group; exchange of a basic residue such as Lysine and Arginine with another basic residue; and replacement of an aromatic residue such as Phenylalanine, Tyrosine with another aromatic residue.

Further guidance regarding what amino acid substitutions could be made to make the genus of amylase-encoding nucleic acids of the invention can be found, e.g., in paragraph [0054], page 10, of the specification:

> [0054] Additionally a "substantially identical" amino acid sequence is a sequence that differs from a reference sequence by one or more conservative or non-conservative amino acid substitutions, deletions, or insertions, particularly when such a substitution occurs at a site that is not the active site of the molecule, and provided that the polypeptide essentially retains its functional properties. A conservative amino acid substitution, for example, substitutes one amino acid for another of the same class (*e.g.*, substitution of one hydrophobic amino acid, such as isoleucine, valine, leucine, or methionine, for another, or substitution of one polar amino acid for another, such as substitution of arginine for lysine, glutamic acid for aspartic acid or glutamine for asparagine). One or more amino acids can be deleted, for

> example, from an esterase polypeptide, resulting in modification of the structure of the polypeptide, without significantly altering its biological activity. For example, amino- or carboxyl-terminal amino acids that are not required for esterase biological activity can be removed. Modified polypeptide sequences of the invention can be assayed for esterase biological activity by any number of methods, including contacting the modified polypeptide sequence with an esterase substrate and determining whether the modified polypeptide decreases the amount of specific substrate in the assay or increases the bioproducts of the enzymatic reaction of a functional esterase polypeptide with the substrate.

Accordingly, the specification did provide guidance as to what base and residue changes could be made to make the genus of amylase-encoding nucleic acids of the invention.

Furthermore, Applicants respectfully aver that, if desired, direction and guidance to the skilled artisan as to which base (and amino acid residues) may be modified to obtain a structural or functional esterase variant was also readily available in the art at the time of the invention. While not necessary, but if desired, one skilled in the art at the time of the invention had many sources of guidance, in addition to the specification, to determine which bases (amino acid residues) of a sequence of the invention could be modified to make, identify, screen for and use structural and/or functional variants of the exemplary SEQ ID NO:26 or SEQ ID NO:36 without undue experimentation. For example, active sites and structures of various polypeptides having esterase activity had been described, e.g., by Ghosh (1995) Structure 3:279-288; Liang (1993) European J. Biochem. 211:821-827; Krebs (1993) J. Biol. Chem. 268:948-954; Toone, et al., "Enzymes in Organic Synthesis. 49. Resolution of Racemic Monocyclic Esters with Pig Liver Esterase", Tetrahedron Asym., 1991, 2:207. See also Ghosh (2001) J. Biol. Chem. 276:11159-11166, Epub 2000 Dec 29; Wei (1999) Nat. Struct. Biol. 6:340-345.

Accordingly, one skilled in the art at the time of the invention, using the teaching of the specification had many sources of direction to determine which amino acid residues could be substituted, deleted or inserted into an exemplary nucleic acid to obtain a genus of esterases of the invention.

The Specification Provides Reasonable Enablement

However, assuming *arguendo* that a *prima facie* case of nonenablement was made, Applicants respectfully maintain that the instant specification does provide reasonable enablement commensurate with the scope of the claimed invention. The Office alleges, inter alia, that because there is a large number of possible nucleic acid sequence variations of the exemplary SEQ ID NO:26, it would take undue experimentation to determine all of the active, versus inactive, species within the claimed genus. The Office appears to setting an erroneous standard that the specification must enable the skilled artisan to routinely identify *every* possible active variant of the exemplary sequence of the invention (see, e.g., page 19, lines 1 to 6, of the OA).

However, the proper test for enablement is not that the specification must teach a method(s) for identifying *every* possible specie of a broadly claimed genus. The proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims. See, e.g., In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). See MPEP §2164.08, pg 2100-197, 8th ed., rev. 2, May 2004. `The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' " In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). MPEP §2164.06, pg 2100-192, 8th ed., rev. 2, May 2004.

The facts in In re Wands are sufficiently analogous to the instant scenario to help illustrate this point, as explained in the MPEP (§2164.06(b), pg 2100-195, 8th ed., rev. 2, May 2004):

> (B) In In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), the court reversed the rejection for lack of enablement under 35 U.S.C. 112, first paragraph, concluding that undue experimentation would not be required to practice the invention. The nature of monoclonal antibody technology is such that experiments first involve the entire attempt to make monoclonal hybridomas to determine which ones secrete antibody with the desired characteristics. The court found that the specification provided considerable direction and guidance on how to practice the claimed invention and presented

> working examples, that all of the methods needed to practice the invention were well known, and that there was a high level of skill in the art at the time the application was filed. Furthermore, the applicant carried out the entire procedure for making a monoclonal antibody against HBsAg three times and each time was successful in producing at least one antibody which fell within the scope of the claims.

In In re Wands, after considering all the factors related to the enablement issue, the court concluded that "it would not require undue experimentation to obtain antibodies needed to practice the claimed invention." Id., 8 USPQ2d at 1407. In In re Wands, it was not necessary to provide a method to routinely identify *every* monoclonal antibody hybridoma made in any particular production round, or *every possible* monoclonal antibody that could bind the exemplary antigen. Nor was it necessary to produce a working specie after very antibody-making procedure. In fact, in In re Wands, the screening protocol was found sufficiently enabling even though only one antibody was identified after running three procedures.

Contrary to the test set forth in In re Wands, the Office erroneously sets a standard for undue experimentation requiring a protocol where *every* possible variant of the exemplary enzyme of the invention must be identified. The proper legal test is that the scope of enablement must only bear a "reasonable correlation" to the scope of the claims.

In fact, the instant specification does provide reasonable enablement commensurate with the scope of the claimed invention. For example, as in In re Wands, at the time of the invention it only entailed relatively straightforward and routine protocols to make and identify variants of the exemplary enzyme of this invention. Determining whether any particular enzyme or nucleic acid fell with the scope of the claimed invention was a very straightforward and routine procedure; as discussed in detail in Applicants' November 19, 2003, response (pages 21 to 23) and Dr. Jay Short's expert declaration. All of the protocols needed to practice the invention were well known and there was a high level of skill in the art at the time the application was filed.

Also analogous to In re Wands, the instant specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples. For example, in Example 4, pages 73 to 74, the specification provides a detailed exemplary esterase

activity screening protocol. Additionally, paragraph [0274], page 69, notes the high state of the art at the time of the invention regarding screening protocols: "[m]any of the procedural steps are performed using robotic automation enabling the execution of many thousands of biocatalytic reactions and screening assays per day as well as ensuring a high level of accuracy and reproducibility." Batch screening of sample is described, inter alia, on page 15, paragraph [0075]:

> In another embodiment, the method provides that the gene reassembly process is performed systematically, for example to generate a systematically compartmentalized library, with compartments that can be screened systematically, *e.g.*, one by one. In other words the invention provides that, through the selective and judicious use of specific nucleic acid building blocks, coupled with the selective and judicious use of sequentially stepped assembly reactions, an experimental design can be achieved where specific sets of progeny products are made in each of several reaction vessels. This allows a systematic examination and screening procedure to be performed. Thus, it allows a potentially very large number of progeny molecules to be examined systematically in smaller groups. (emphasis added)

Accordingly, because the specification provided considerable direction and guidance on how to practice the claimed invention and presented working examples, and all of the methods needed to practice the invention were well known, and there was a high level of skill in the art at the time the application was filed, the instant specification does provide reasonable enablement commensurate with the scope of the claimed invention.

Applicants wish to emphasize that the amount of time needed and the difficulty in screening are not determinative of enablement undue experimentation if the experimentation is routine. Enablement is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive. Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984); W.L. Gore and Associates v. Garlock, Inc., 721 F.2d 1540, 1556, 220 USPQ 303, 315 (Fed. Cir. 1983). Experimentation is not considered undue, even if extensive, if it is routine or if the specification provides reasonable guidance regarding the direction of experimentation -- time and difficulty are not determinative of undue experimentation if the experimentation is routine (emphasis added). See PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ2d 1618, 1623 (Fed. Cir.

1996); In re Wands, 858 F.2d at 736-40, 8 USPQ2d at 1403-7; Hybritech, Inc. v. Monoclonal Antibodies, Inc.,802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987) (acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."). Thus, enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue."

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." As set forth in In re Wands, these factors include, but are not limited to: The breadth of the claims; The nature of the invention; The state of the prior art; The level of one of ordinary skill; The level of predictability in the art; The amount of direction provided by the inventor; The existence of working examples; and, The quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). MPEP §2164.01(a), pg 2100-185, 186, 8th ed., rev. 2, May 2004. Applicants respectfully aver that taking into consideration all of these factors and all of the evidence and argument presented to the Office, the pending claims are sufficiently enabled by the specification to meet the requirements of 35 U.S.C. §112, first paragraph.

In light of Applicants' remarks in this and earlier responses, including the submitted expert declaration by Dr. Jay Short, Applicants respectfully submit that the specification provides sufficient enablement to meet the requirements of 35 U.S.C. § 112, first paragraph, and the rejection can be properly withdrawn.

Issues Under 35 U.S.C. § 102 (b)

Claims 3, 5-15, 67-84, 93-97, 103-105, and 107-109 are rejected under 35 U.S.C. § 102 (b) as allegedly being anticipated by Robertson et al., WO 97/30160.

However, as discussed above, the instant amendment perfects the instant application's claim to priority to PCT/US97/02039, filed February 11, 1997, published in English on August 21, 1997 as WO 97/30160, as discussed in the "Decision on Petition under 37 CFR 1.78(a)(3)", mailed May 28, 2004. Accordingly, Robertson et al., WO 97/30160, is not prior art to the instant application, and the rejection under section 102(b) can be properly withdrawn.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants respectfully aver that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs and 35 U.S.C. §102(b). In view of the above, claims in this application after entry of the instant amendment are believed to be in condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 564462000820.

As noted above, Applicants have requested a telephone conference with the undersigned representative to expedite prosecution of this application. After the Examiner has reviewed the instant response and amendment, please telephone the undersigned at 858 720 5133.

Dated: November 3, 2005

Respectfully submitted,

By _____

Gregory P. Einhorn
Registration No.: 38,440
MORRISON & FOERSTER LLP
12531 High Bluff Drive
Suite 100
San Diego, California 92130-2040
(858) 720-5133

sd-286341

Docket No.: 564462000820
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Dan E. ROBERTSON et al.

Application No.: 09/903,410

Art Unit: 1652

Filed: July 10, 2001

Examiner: R. Prouty

For: ENZYMES HAVING ESTERASE ACTIVITY AND METHODS OF USE THEREOF

PETITION TO ACCEPT UNINTENTIONALLY DELAYED CLAIM FOR PRIORITY UNDER 35 U.S.C. § 365(c)

Mail Stop Petition
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicants hereby petition for entry of the enclosed Amendment claiming benefit under 35 U.S.C. § 365(c) of International Application No. PCT/US97/02039, filed February 11, 1997 and published as WO 97/30160. The present application is directed to enzymes having esterase activity and methods of use thereof; aspects of this were described in International Application No. PCT/US97/02039. The applications contain at least one inventor in common and the PCT application discloses the invention claimed herein.

Applicants hereby state that the entire delay between the date the claim for benefit was due under 37 C.F.R. § 1.78(a)(5) and the date of the present amendment was unintentional.

Entry of the Amendment and accordation of benefit are respectfully requested.

sd-197699

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 564462000820.

Dated: May 13, 2004

Respectfully submitted,

By _____
Laurie L. Hill, Ph.D.
Registration No.: 51,804
MORRISON & FOERSTER LLP
3811 Valley Centre Drive, Suite 500
San Diego, California 92130
(858) 720-7955

COPY

sd-197699